REMARKS

This amendment is in response to the Office Communication mailed March 08, 2005, and supplements Applicants response of October 27, 2004, which is expressly incorporated herein, which was in response to the non-final Office Action on the merits mailed May 27, 2004.

In the Office Communication mailed March 08, 2005, the Patent Office alleges that the claim amendments made in Applicants' last response – that of October 27, 2004 – were not based on currently pending claims (i.e., the claim amendments of October 27, 2004, were not based on Applicants' response of March 18, 2004), but rather were inadvertently based on Applicants' earlier response of September 15, 2003 (this response was actually mailed on September 12, 2003).

However, Applicants respectfully submit that the claim amendments made in Applicants' last response – that of October 27, 2004 – were properly based on pending claims (i.e., they were based on Applicants' response of March 18, 2004); and in support submit herein a copy of Applicants' last response (of October 27, 2004).

Telephonic interview

Applicants respectfully request a telephonic interview to discuss substantive issues after the Examiner has reviewed the instant response and amendment. Please call Applicants' representative, Gregory Einhorn, at (858) 720-5133.

CONCLUSION

In view of the remarks as set forth herein and in Applicants' response and amendment of October 27, 2004, Applicants respectfully aver that the Examiner can properly withdraw the rejection of the pending claims under 35 U.S.C. §112, first and second paragraphs and 35 U.S.C. §102(e). The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Applicants submit concurrently herewith a Petition for 2-month Extension of Time and the appropriate Fee Transmittal for the Petition. No other fees are believed to be necessitated by the present response and amendment. However, in the event any such fees are due, the Commissioner is hereby authorized to charge any such fees to Deposit Account No. 03-1952 referencing docket no. 577122000200. Please credit any overpayment to this account.

As noted above, Applicants have requested a telephone conference with the undersigned representative to expedite prosecution of this application. After the Examiner has reviewed the instant response and amendment, please telephone the undersigned at (858) 720-5133.

Dated: June 8, 2005

Respectfully submitted,

By

Gregory P. Einhorn
Registration No.: 38,440
MORRISON & FOERSTER LLP
3811 Valley Centre Drive
Suite 500
San Diego, California 92130-2332
(858) 720-5133

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MORRISON & FOERSTER LLP
Attorneys at Law
3811 Valley Centre Drive, Suite 500
San Diego, California 92130-2332
Telephone: (858) 720-5100
Facsimile: (858) 720-5125

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Comments:

Attorney Docket:	577122000200
Group Art Unit:	1654
Examiner:	B. Chiam
Serial No.:	09/719,889
Filing Date:	(Int'l) June 18, 1999
Inventor(s):	Earl R. OWEN et al.
Title:	METHOD OF TISSUE REPAIR II

Papers attached:
1. Transmittal Form (1 page)
2. Fee Transmittal (1 page + duplicate for fee processing)
3. Petition for 2-month Extension of Time (1 page)
4. Amendment in Response to Office Action of May 27, 2004 (24 pages)

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PAGE 1/28 * RCVD AT 10/27/2004 9:10:21 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/2 * DNIS:8729306 * CSID:858 720 5125 * DURATION (mm-ss):12-09

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3811 Valley Centre Drive, Suite 500
San Diego, California 92130-2332
Telephone: (858) 720-5100
Facsimile: (858) 720-5125

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Attorney Docket:	577122000200
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Telephone: (858) 720-5100
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	09/719,889
Filing Date	(Int'l) June 18, 1999
First Named Inventor	Earl R. OWEN
Art Unit	1654
Examiner Name	B. Chism
Total Number of Pages in This Submission: 29	Attorney Docket Number: 577122000200

ENCLOSURES (*Check all that apply*)

- [X] Fee Transmittal Form (1 page + duplicate)
- [ ] Fee Attached
- [X] Amendment/Reply (24 pages)
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [X] Extension of Time Request (1 page)
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
- [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
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- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] After Allowance communication to Technology Center (TC)
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
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- [ ] Status Letter
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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	MORRISON & FOERSTER LLP Gregory P. Einhorn - 38,440
Signature	
Date	October 27, 2004

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FEE TRANSMITTAL for FY 2005

Effective 10/01/2004. Patent fees are subject to annual revision.

[X] Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 632.00

Complete if Known	
Application Number	09/719,889
Filing Date	(Int'l) June 18, 1999
First Named Inventor	Earl R. OWEN
Examiner Name	B. Chism
Art Unit	1654
Attorney Docket No.	577122000200

METHOD OF PAYMENT *(check all that apply)*

[ ] Check [ ] Credit Card [ ] Money Order [ ] Other [ ] None

[X] Deposit Account:

Deposit Account Number: 03-1952

Deposit Account Name: Morrison & Foerster LLP

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[X] Charge any additional fee(s) or any underpayment of fee(s)

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	790	2001	395	Utility filing fee	
1002	350	2002	175	Design filing fee	
1003	550	2003	275	Plant filing fee	
1004	790	2004	395	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($) 0.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

			Extra Claims		Fee from below		Fee Paid
Total Claims	95	-78** =	17	x	9	=	153.00
Independent Claims	9	-3** =	6	x	44	=	264.00
Multiple Dependent						=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	88	2201	44	Independent claims in excess of 3
1203	300	2203	150	Multiple dependent claim, if not paid
1204	88	2204	44	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 417.00

***or number previously paid, if greater; For Reissues, see above*

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge – late filing fee or oath	
1052	50	2052	25	Surcharge – late provisional filing fee or cover sheet.	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	430	2252	215	Extension for reply within second month	215.00
1253	980	2253	490	Extension for reply within third month	
1254	1,530	2254	765	Extension for reply within fourth month	
1255	2,080	2255	1,040	Extension for reply within fifth month	
1401	340	2401	170	Notice of Appeal	
1402	340	2402	170	Filing a brief in support of an appeal	
1403	300	2403	150	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive – unavoidable	
1453	1,330	2453	665	Petition to revive – unintentional	
1501	1,370	2501	685	Utility issue fee (or reissue)	
1502	490	2502	245	Design issue fee	
1503	660	2503	330	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	790	2809	395	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	790	2810	395	For each additional invention to be examined (37CFR 1.129(b))	
1801	790	2801	395	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	
Other fee (specify)					

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 215.00

SUBMITTED BY				(Complete *(if applicable)*)	
Name (Print/Type)	Gregory P. Einhorn	*Registration No. (Attorney/Agent)*	38,440	*Telephone*	(858) 720-5133
Signature				*Date*	October 27, 2004

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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) 577122000200

In re Application of	Earl R. OWEN et al.
Application Number 09/719,889	Filed (Int'l) June 18, 1999
For	METHOD OF TISSUE REPAIR II
Art Unit 1654	Examiner B. Chism

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and appropriate non-small-entity fee are as follows (check time period desired):

☐	One month (37 CFR 1.17(a)(1))	$
☒	Two months (37 CFR 1.17(a)(2))	$ 430.00
☐	Three months (37 CFR 1.17(a)(3))	$
☐	Four months (37 CFR 1.17(a)(4))	$
☐	Five months (37 CFR 1.17(a)(5))	$

☒ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee amount shown above is reduced by one-half, and the resulting fee is: $ 215.00 .

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 03-1952 .

~~I have enclosed a duplicate copy of this sheet~~. Fee Transmittal form (PTO/SB/17) is attached to this submission in duplicate.

I am the

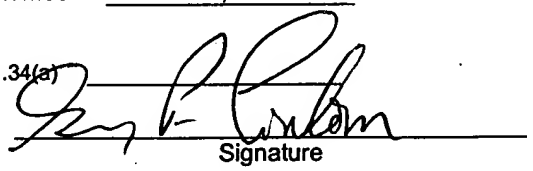
☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

☒ attorney or agent of record. Registration Number 38,440

☐ attorney or agent under 37 CFR 1.34(a).
Registration number if acting under 37 CFR 1.34(a)

October 27, 2004
Date


Signature

(858) 720-5133
Telephone Number

Gregory P. Einhorn
Typed or printed name

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below

☒ Total of 1 forms are submitted.

sd-227297

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Dated: October 27, 2004 Signature: Norman Green (Norman Green)

Docket No.: 577122000200 / 30347USP00 (PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Earl R. OWEN et al.

Application No.: 09/719,889 Art Unit: 1654

Filed: (Int'l) June 18, 1999 Examiner: B. Chism

For: METHOD OF TISSUE REPAIR II

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

INTRODUCTORY COMMENTS

Applicants respectfully request entry of the amendment and consideration of the remarks set forth herein. A non-final Office Action on the merits was mailed May 27, 2004. A response was initially due August 27, 2004. Applicants herein submit a petition for a two month extension of time to October 27, 2004, under 37 C.F.R. §1.136, with the appropriate fee under 37 C.F.R. §1.17. Accordingly, this Response is timely filed.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 16 of this paper.

AMENDMENTS TO THE CLAIMS

Please amend the claims as follows.

This listing of claims will replace all prior versions, and listing, of claims in the application:

1. (currently amended) A biomolecular solder ~~comprising a proteinaceous substance~~ made by a method comprising

(b) providing a composition comprising a proteinaceous substance in a solvent; and

(b) pre-denaturing the proteinaceous substance before placing the composition *in situ* by at least partially denaturing the proteinaceous substance while moist with the solvent such that at least a portion of the proteinaceous substance bonds together ~~and, (c) shaping the proteinaceous substance, wherein the solder is shaped before, during or after the denaturing of step (b), or a combination thereof, and, when shaped, the final shape of the solder is essentially maintained and the solubility of the proteinaceous substance is reduced in a physiological fluid at body temperature~~.

2. (previously presented) A solder according to claim 1 wherein the proteinaceous substance comprises a protein.

3. (currently amended) A solder according to claim 2 wherein the protein comprises ~~is any one of~~ an albumin, a collagen, an elastin, a fibrinogen, or any combination thereof.

4. (previously presented) A solder according to claim 1, further comprising a dye.

5. (currently amended) A solder according to claim 4 wherein the dye comprises an indocyanine green, a methylene blue or a fluorescein isothiocyanate or any combination thereof.

6. (previously presented) A solder according to claim 1, further comprising an adjuvant.

7. (currently amended) A solder according to claim 1 further comprising ~~6 wherein the adjuvant is selected from the group consisting of~~ a growth factor, a sodium hyaluronate, a hormone and an anti-coagulant.

8. (previously presented) A solder according to claim 1 further comprising a material for improving the strength of the solder.

9. (previously presented) A solder according to claim 8 wherein the material comprises a polytetrafluoroethylene fibre or a ceramic fibre.

10. (currently amended) A kit comprising a biomolecular solder according to claim 1 ~~any one of claims 1 to 9~~.

11. (currently amended) A method of preparing a biomolecular solder *ex vivo*, the method comprising:

(a) providing a composition ~~biomolecular solder~~ comprising a proteinaceous substance and a solvent;

(b) shaping the composition ~~solder~~ into a desired shape, wherein the composition ~~solder~~ is shaped before, during or after the pre-denaturing ~~denaturing~~ of step (c), or a combination thereof; and

(c) pre-denaturing ~~denaturing~~ the proteinaceous substance before placing the composition *in situ* by at least partially denaturing the proteinaceous substance while the composition ~~solder~~ is moist such that at least a portion of the proteinaceous substance bonds together, thereby preparing a biomolecular solder ~~and the desired shape of the solder is essentially maintained and the solubility of the proteinaceous substance is reduced in a physiological fluid at body temperature~~.

12. (currently amended) A method according to claim 11 wherein the proteinaceous substance is pre-denatured ~~denatured~~ by exposing the solder to an energy for a time period that is sufficient to allow the energy to at least partially denature the proteinaceous substance.

13. (currently amended) A method according to claim 12 wherein the energy [[is]] comprises a thermal energy.

14. (currently amended) A method according to claim 13 [[11]] wherein the proteinaceous substance is pre-denatured ~~denatured~~ by heating the solder at a temperature of greater than 40°C for a time period of about 30 seconds or longer.

15. (currently amended) A method according to claim 14 [[or 32]] wherein in the pre-denaturing step the solder is heated in a hot liquid bath or in pressurized steam.

16. (currently amended) A method according to claim 11 wherein the proteinaceous substance is pre-denatured ~~denatured~~ by exposure ~~exposing the solder~~ to a denaturing agent for a time period that is sufficient to allow the denaturing agent to homogenously and completely denature the proteinaceous substance.

17-18. (canceled)

19. (currently amended) A method according to claim 11 wherein the biomolecular solder further comprises a dye ~~for improving energy deposition~~.

20. (previously presented) A method according to claim 19 wherein the dye is in an amount between 0.1 to 2.5% w/w of the solder.

21. (currently amended) A method according to claim 19 [[20]] wherein the dye is mixed with the solvent, prior to mixing the solvent with the proteinaceous substance.

22. (currently amended) A method according to claim 11 wherein the pre-denaturing step further comprises ~~comprising~~ drying the composition ~~solder~~, wherein a majority of the solvent is removed from the composition ~~solder~~ during the drying of the composition ~~solder~~.

23. (canceled)

24. (currently amended) The [[A]] method of ~~according to~~ claim 11 wherein in the pre-denaturing step the composition ~~solder~~ is applied to a support structure before the proteinaceous substance is pre-denatured ~~denatured~~.

25. (currently amended) The [[A]] method of ~~according to~~ claim 24 wherein the support structure is a mesh, a stiffener or a graft material.

26. (currently amended) The [[A]] method of ~~according to~~ claim 11 further comprising the step of sterilizing the biomolecular solder following the pre-denaturing ~~denaturing~~ of the proteinaceous substance.

27. (currently amended) A method of welding or joining a biological tissue together, the method comprising:

(a) applying a biomolecular solder according to claim 1 to the biological tissue to be welded or joined together; and

(b) exposing the biomolecular solder to an energy for a time sufficient to cause the solder to weld or join the biological tissue together.

28. (currently amended) The [[A]] method of ~~according to~~ claim 27 wherein the pre-denatured solder is moistened before application to the biological tissue.

29. (currently amended) The biomolecular [[A]] solder of ~~according to~~ claim 1 wherein the proteinaceous substance is denatured *ex vivo* such that it is essentially insoluble in the physiological fluid at body temperature.

30. (currently amended) The biomolecular [[A]] solder of ~~according to~~ claim 1 wherein the pre-denatured solder has been shaped from a composition comprising the proteinaceous substance in an amount of at least 40% w/w of the composition.

31. (currently amended) The biomolecular [[A]] solder of ~~according to~~ claim 1 wherein the proteinaceous substance comprises at least one substance selected from the group consisting of a protein, a polypeptide, a mixture of proteins, a biodegradable protein, a fibrous material, a synthetic polypeptide and ~~analogues~~ any combination thereof.

32. (currently amended) The [[A]] method of ~~according to~~ claim 11 further comprising drying the pre-denatured solder ~~following the denaturation of the proteinaceous substance~~.

33. (currently amended) The [[A]] method of ~~according to~~ claim 11 wherein the pre-denatured solder, shaped into the predetermined shape, comprises the proteinaceous substance in an amount of at least 40% w/w or greater of the solder.

34. (currently amended) The [[A]] method of ~~according to~~ claim 11, wherein the solder initially comprises a proteinaceous substance in an amount in the range from 50% w/w to 80% w/w of the solder.

35. (currently amended) The [[A]] method of ~~according to~~ claim 33 or 34 wherein the solder initially comprises a solvent in an amount up to 60% w/w [[w/w/]] of the solder.

36. (currently amended) The [[A]] method of ~~according to~~ claim 11 [[14]] wherein the pre-denaturing step comprises heating the solder ~~is heated~~ at a temperature in a range from between about 75°C to 100°C.

37. (currently amended) The [[A]] method of ~~according to~~ claim 36 wherein the pre-denaturing step comprises heating the solder ~~is heated~~ at a temperature in a range from between about 100°C to 150°C.

38. (currently amended) The [[A]] method of ~~according to~~ claim 16 wherein in the pre-denaturing step the denaturing agent comprises a chemical.

39. (currently amended) The [[A]] method of claim ~~according to any one of claims~~ 11, [[32, or 33]] wherein the proteinaceous substance comprises at least one substance selected from the group consisting of a protein, a polypeptide, a mixture of proteins, a biodegradable protein, a fibrous material, a synthetic polypeptide and ~~analogues~~ any combination thereof.

40. (currently amended) The [[A]] method of ~~according to~~ claim 39 wherein the proteinaceous substance comprises at least one substance selected from the group consisting of human albumin, bovine albumin, horse albumin, ovine albumin, rabbit albumin, rat albumin, and a combination thereof ~~a protein and a polypeptide~~.

41. (currently amended) The [[A]] method of ~~according to~~ claim [[40]] 39, wherein the proteinaceous substance comprises at least one protein selected from the group consisting of an albumin, an elastin, a collagen and a fibrinogen.

42. (currently amended) The [[A]] method of ~~according to~~ claim 28 wherein the moistening of the pre-denatured solder increases flexibility of the solder.

43. (previously presented) The biomolecular solder of claim 1, wherein the solvent comprises an aqueous solvent.

44. (previously presented) The biomolecular solder of claim 43, wherein the aqueous solvent comprises water or saline.

45. (previously presented) The method of claim 11, wherein the solvent comprises an aqueous solvent.

46. (previously presented) The method of claim 45, wherein the aqueous solvent comprises water or saline.

47. (currently amended) The method of claim 11, wherein denaturing the protein *in situ* in step (e) comprises denaturing the proteinaceous substance ~~is denatured~~ by exposing the solder to a laser energy.

48. (previously presented) The method of claim 47, wherein the laser is a diode laser.

49. (previously presented) The method of claim 27, wherein the biological tissue is welded together to effect a repair.

50. (currently amended) The biomolecular solder of claim 1, wherein denaturing the protein *in situ* in step (e) comprises denaturing all of the proteinaceous substance ~~is denatured~~.

51. (currently amended) The biomolecular solder of claim 1, wherein denaturing the protein *in situ* in step (e) comprises denaturing a portion of the proteinaceous substance ~~is denatured~~.

52. (currently amended) The method of claim 11, wherein denaturing the protein *in situ* in step (e) comprises denaturing all of the proteinaceous substance ~~is denatured~~.

53. (currently amended) The method of claim 11, wherein denaturing the protein *in situ* in step (e) comprises denaturing a portion of the proteinaceous substance ~~is denatured~~.

54. (currently amended) The biomolecular solder of claim 1, wherein the method of making the solder further comprises sterilizing the biomolecular solder before the step (d) placing of the pre-denatured solder *in situ*.

55. (currently amended) The biomolecular solder of claim 1, wherein the pre-denatured proteinaceous substance is shaped into a sheet, a tube, a partial tube, a strip, a patch, a hollow tube with a flanged end or a rod before the step (d) placing of the pre-denatured solder *in situ*, after the step (d) placing the pre-denatured solder *in situ*, or a combination thereof.

56. (currently amended) The method of claim 11, the desired shape comprises a sheet, a tube, a partial tube, a strip, a patch, a hollow tube with a flanged end or a rod before the step (d) placing of the pre-denatured solder *in situ*, after the step (d) placing the pre-denatured solder *in situ*, or a combination thereof.

57. (currently amended) A biomolecular solder comprising a protein comprising an albumin, an elastin, a collagen, a fibrinogen or a combination thereof, wherein the biomolecular solder is made by the method of claim 1, and the pre-denatured solder ~~proteinaceous substance that~~ has been at least partially denatured while moist such that the protein ~~proteinaceous substance~~ bonds together and, when shaped, the shape of the solder is thereby essentially maintained and the solubility of the protein ~~proteinaceous substance~~ is reduced in a physiological fluid at body temperature.

58. (currently amended) The biomolecular solder of claim 57, wherein the solder is shaped before pre-denaturing ~~denaturation~~.

59. (currently amended) The biomolecular solder of claim 57, wherein the solder is shaped after pre-denaturing ~~denaturation~~.

60. (currently amended) The biomolecular solder of claim 57, wherein the protein ~~proteinaceous substance~~ comprises a bovine, rabbit, ovine, rat or horse serum albumin ~~protein~~.

61. (currently amended) The biomolecular solder of claim 57 [[60]], wherein the protein comprises a human [[an]] albumin, a human [[an]] elastin, a human fibrinogen, a human collagen or any combination thereof.

62. (previously presented) The biomolecular solder of claim 57, further comprising a dye for improving energy deposition into the solder when the solder is exposed to energy.

63. (previously presented) The biomolecular solder of claim 57, wherein the proteinaceous substance has been at least partially denatured while moist with a solvent.

64. (previously presented) The biomolecular solder of claim 63, wherein the solvent comprises an aqueous solvent.

65. (previously presented) The biomolecular solder of claim 64, wherein the aqueous solvent comprises water or saline.

66. (new) A biomolecular solder made by a method comprising:

(a) providing a composition comprising a protein in a solvent;

(b) pre-denaturing the protein before placing the composition *in situ* by at least partially denaturing the protein while moist with the solvent such that at least a portion of the protein bonds together; and,

(c) shaping the pre-denatured protein, wherein the solder is shaped before, during or after the pre-denaturing of step (b), or a combination thereof.

67. (new) The biomolecular solder of claim 66, further comprising steps

(d) placing the pre-denatured solder *in situ*, and

(e) further denaturing the protein *in situ* such that the final shape of the *in situ*-denatured solder is essentially maintained and the solubility of the protein is reduced in a physiological fluid at body temperature.

68. (new) The biomolecular solder of claim 66, wherein the protein comprises albumin.

69. (new) The biomolecular solder of claim 68, wherein the albumin comprises human albumin, bovine albumin, ovine albumin, horse albumin, rat albumin or a mixture thereof.

70. (new) The biomolecular solder of claim 66, wherein the protein comprises collagen, elastin, fibrinogen or a combination thereof.

71. (new) The biomolecular solder of claim 66, wherein pre-denaturing the protein before placing the composition *in situ* comprises the step of steam heating or immersion into hot water.

Claim 72. (new) The biomolecular solder of claim 71, wherein the steam heating step comprises use of a temperature of between about 100°C and 150°C.

73. (new) The biomolecular solder of claim 66, wherein pre-denaturing the protein before placing the composition *in situ* comprises use of light, heat, radiation, ultrasound or chemicals.

74. (new) The biomolecular solder of claim 66, wherein the step of denaturing the protein *in situ* comprises exposing the solder to light, heat, radiation, ultrasound or chemicals.

75. (new) The biomolecular solder of claim 66, wherein the step of denaturing the protein *in situ* comprises exposing the solder to a laser energy.

76. (new) The biomolecular solder of claim 75, wherein the laser energy that denatures the protein *in situ* comprises a power of about 90 mW and a wavelength of about 805 nm.

77. (new) The biomolecular solder of claim 75, wherein the laser energy that denatures the protein *in situ* comprises a spot size at the solder of about 200 μm.

78. (new) The biomolecular solder of claim 66, wherein further comprising a dye.

79. (new) The biomolecular solder of claim 78, wherein the dye comprises an indocyanine green, a methylene blue or a fluorescein isothiocyanate.

80. (new) The method of claim 27, wherein the biological tissue is a human or an animal tissue.

81. (new) The method of claim 27, wherein a blood vessel, a nerve, a pancreatic duct, a liver vessel or duct, a cystic duct, a tear duct, prostatic duct, a ureter, urethra, an epididymis, a vas deferens, a fallopian tube, a bowel, a bronchi, a gastroenterological tube or duct, a respiratory tube or duct or a brain vessel, tube or duct are welded together.

82. (new) A solder according to claim 1, wherein in step (b) the proteinaceous substance is fully denatured.

83. (new) The biomolecular solder of claim 1 wherein the composition comprises a proteinaceous substance in a concentration in a range of between about 40% w/w and 80% w/w, or between about 45% w/w and 75% w/w, of the composition.

84. (new) A biomolecular solder made by a method comprising

(a) providing a composition comprising a proteinaceous substance in a solvent;

(b) pre-denaturing the proteinaceous substance before placing the composition *in situ* by at least partially denaturing the proteinaceous substance while moist with the solvent such that at least a portion of the proteinaceous substance bonds together and the solubility of the proteinaceous substance is reduced in a physiological fluid at body temperature; and,

(c) shaping the proteinaceous substance, wherein the solder is shaped before, during or after the denaturing of step (b), or a combination thereof, and, when shaped, the final shape of the solder is essentially maintained.

85. (new) A sterile biomolecular solder made by a method comprising

(a) providing a composition comprising a proteinaceous substance in a solvent;

(b) pre-denaturing the proteinaceous substance *ex vivo* by at least partially denaturing the proteinaceous substance while moist with the solvent such that at least a portion of the proteinaceous substance bonds together; and,

(c) sterilizing the pre-denatured solder.

86. (new) A composition comprising a shaped proteinaceous substance and a solvent, wherein the proteinaceous substance is at least partially denatured *ex vivo* while moist with the solvent such that at least a portion of the proteinaceous substance bonds together.

87. (new) The composition of claim 86, wherein the proteinaceous substance is fully denatured.

88. (new) The composition of claim 86, wherein the protein comprises an albumin, a collagen, an elastin, a fibrinogen, or any combination thereof.

89. (new) A sterile shaped biomolecular solder comprising an at least partially cross-linked proteinaceous substance and a solvent, wherein the proteinaceous substance is at least partially cross-linked while moist with the solvent such that at least a portion of the proteinaceous substance bonds together.

90. (new) A biomolecular solder comprising an at least partially cross-linked protein and a solvent, wherein the protein comprises an albumin, a collagen, an elastin, a fibrinogen, or any combination thereof, and is at least partially cross-linked while moist with the solvent.

91. (new) A kit comprising the sterile biomolecular solder of claim 85.

92. (new) A kit comprising the sterile shaped biomolecular solder of claim 89.

93. (new) A kit comprising the biomolecular solder of claim 90.

94. (new) A kit comprising the sterile biomolecular solder of claim 85, the sterile shaped biomolecular solder of claim 89 or the biomolecular solder of claim 90, and instructions for using the solder as set forth in claim 27.

REMARKS

Status of the Claims

Pending claims

Claims 1 to 16, 19 to 22 and 24 to 65 are currently pending.

Claims added in the instant amendment

In the present response, claims 66 to 94 are added. Accordingly, after the entry of the instant amendment, claims 1 to 16, 19 to 22 and 24 to 94 will be pending and under examination.

Outstanding Rejections

Claims 1, 27, 57 to 60 and 63 are rejected under the written description requirement of 35 U.S.C. 112, first paragraph. The rejection of claims 31 and 39 under 35 U.S.C. 112, second paragraph, has been maintained (and claims 2 to 10, 27 to 31, 40 to 44, 49 to 51, 54, 55, 61, 62, 64, 65 are rejected under 35 U.S.C. 112, second paragraph, as depending from rejected claims). Claims 1 to 7, 27 to 31, 43, 44, 49 and 57 to 63 are rejected under 35 U.S.C. 102(e) as allegedly anticipated by Lauto et al. 2001 (U.S. Patent 6,323,037 B1), filed April 6, 1999 (hereinafter "Lauto"). Applicants respectfully traverse all outstanding objections to the specification and rejections of the claims.

Telephonic interview

Applicants respectfully request a telephonic interview to discuss substantive issues after the Examiner has reviewed the instant response and amendment. Please call Applicants' representative Gregory Einhorn at 858 720 5133.

Support for the Claim Amendments

The specification sets forth an extensive description of the invention in the new and amended claims. For example, support for claims directed to biomolecular solders, and methods for making and using them, comprising pre-denaturing a proteinaceous substance before placing the

solder *in situ* by partially denaturing the proteinaceous substance while moist with a solvent such that at least a portion of the proteinaceous substance bonds together, can be found, inter alia, on page 11, lines 1 to 6; page 14, lines 16 to 34; page 22, lines 4 to 25; page 28, lines 26 to 28, of the specification (i.e., WO 99/65536). Support for claims directed to biomolecular solders, and methods for making and using them, comprising *in situ* denaturation of the solder (after pre-denaturation), can be found, inter alia, on page 11, lines 26 to 35; page 16, lines 3 to 6; page 23, lines 7 to 21; page 24, lines 1 to 34; page 28, line 29 to page 29, line 10. Support for claims directed to biomolecular solders, and methods for making and using them, wherein the solder comprises any one of an albumin, a collagen, an elastin, a fibrinogen, or any combination thereof can be found, inter alia, on page 7, lines 1 to 17. Support for claims directed to biomolecular solders, and methods for making and using them, wherein the solder comprises human, horse, bovine, rat, ovine or rabbit albumin can be found, inter alia, on page 7, lines 10 to 12 and 29 to 30. Support for claims directed to biomolecular solders, and methods for making and using them, wherein the solder is denatured before or after placing the composition *in situ* comprises use of light, heat, radiation, ultrasound or chemicals, can be found, inter alia, on page 8, lines 24 to 29. Support for claims directed to biomolecular solders, and methods for making and using them, wherein the denatured solder is shaped into a sheet, a tube, a partial tube, a strip, a patch, a hollow tube with a flanged end or a rod before or after placing of the pre-denatured solder *in situ*, can be found, inter alia, on page 9, lines 22 to 25. Support for claims directed to methods for using biomolecular solders wherein a blood vessel, a nerve, a pancreatic duct, a liver vessel or duct, a cystic duct, a tear duct, prostatic duct, a ureter, urethra, an epididymis, a vas, a fallopian tube, a bowel, a bronchi, a gastroenterological tube or duct, a respiratory tube or duct or a brain vessel, tube or duct are welded together, can be found, inter alia, on page 16, lines 19 to 21; page 17, lines 28 to 30; page 18, lines 29 to 36. Support for claims directed to biomolecular solders wherein the composition comprises a proteinaceous substance in a concentration in a range of between about 40% w/w and 80% w/w, or between about 45% w/w and 75% w/w, of the composition, can be found, inter alia, on page 7, lines 23 to 34. Support for claims directed to a sterile biomolecular solder, can be found, inter alia, on page 15, lines 34 to 36.

Issues under 35 U.S.C. §112, first paragraph

Written Description

Claims 1, 27, 57 to 60 and 63 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification in such as way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention .

Claim 1, as amended, is directed to biomolecular solders made by a method comprising providing a composition comprising a proteinaceous substance in a solvent; and pre-denaturing the proteinaceous substance before placing the composition *in situ* by at least partially denaturing the proteinaceous substance while moist with the solvent such that at least a portion of the proteinaceous substance bonds together.

In particular, it was alleged that a "broad-brush" discussion of making substances that serve as possible proteinaceous solders does not constitute a disclosure of a representative number of members of that class, and no representative number of claimed solders was disclosed that would lend a full description to the entire class that is entailed by claim 1. It was alleged that the specification's general discussion of making proteinaceous solders constitutes an invitation to experiment by trial and error, and, putting the claimed methods into practice awaited someone actually discovering a necessary component of the invention.

In fact, by setting forth several specific examples of proteinaceous substances that can be used in practicing the claimed invention (e.g., in claim 2, where the proteinaceous substance can comprise a protein, such as (e.g., claim 3) albumin, elastin, collagen, fibrinogen, or any combination thereof), Applicants have met the written description requirement. Applicants have satisfied the written description requirement by showing that their invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, including identifying several exemplary species of proteinaceous substances whose structures are well known in the art (e.g., albumin, elastin, collagen, fibrinogen). In its Guidelines, the PTO has determined that the written description

requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Guidelines, 66 Fed. Reg. at 1106.

Furthermore, the specification described common structural features and common physical properties possessed by all members of the genus of proteinaceous substances used in the claimed methods. The structure of proteinaceous substances, e.g., proteins, such as albumin, elastin, collagen and fibrinogen, were well known in the art. A physical property possessed by all members of the genus is described comprises their ability to bond when denatured, for example, a method comprising denaturing a proteinaceous substance while moist with a solvent such that at least a portion of the proteinaceous substance bonds together. According, the specification set forth a correlation between structure, a physical property possessed by all members of the genus and function.

Because the structure and physical properties (e.g., bonding when denatured) of proteinaceous substances, such as proteins, were well known in the art, disclosure of the use of proteins as proteinaceous substances in the claimed methods alone should be sufficient to meet the written description requirement. However, Applicants have also described several exemplary species (e.g., albumin, elastin, collagen, fibrinogen) of the genus of proteinaceous substances that can be used in the claimed methods, thus providing a specification disclosure that clearly satisfies the written description requirement. In light of disclosure of multiple species of proteinaceous substances that can be used in the claimed methods (e.g., proteins, such as albumin, elastin, collagen, fibrinogen), the Patent Office's remarks that the specification only "constitutes an invitation to experiment" is clearly incorrect.

Furthermore, the specification describes in detail exemplary procedures for practicing the invention. The study described in detail in the specification clearly demonstrates that the claimed methods can be practiced successfully, see, e.g., Example 1, pages 25 to 32 of the

specification (WO 99/65536). Example 1 describes a proof of concept study carried out on 45 subjects (rats) that clearly demonstrates that the methods of the invention can be practiced successfully. It is concluded that "a resorbable protein used as a solder, activated by a diode laser, can provide a reliable, safe and rapid arterial anastomosis, which could be performed by any microsurgeon faster than conventional suturing after a short learning curve" (see page 26, lines 6 to 10). The described exemplary study presents the sutureless, quick and reliable process of the invention that can successfully anastomose small diameter arteries. Because the solders of the invention comprise resorbable protein solders which are at least partially denatured, they can be used to avoid vessel wall fibrosis by eliminating any permanent implanted devices. Accordingly, the Patent Office's remark that the specification only identifies some compounds that might work does not reflect the detailed proof of concept experiments described in the specification.

Issues under 35 U.S.C. §112, second paragraph

Claims 31 and 39 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter that the Applicants regard as the invention (claims 2 to 10, 27 to 31, 40 to 44, 49 to 51, 54, 55, 61, 62, 64, 65 were rejected as depending from rejected claims).

The term "or an analogue thereof" is objected to. The instant amendment addresses this issue.

Issues under 35 U.S.C. §102

Lauto et al. 2001 (U.S. Patent 6,323,037 B1)

Claims 1 to 7, 27 to 31, 43, 44, 49 and 57 to 63 are rejected under 35 U.S.C. 102(e) as allegedly anticipated by Lauto.

The legal standard for anticipation under 35 U.S.C. §102 is one of strict identity. To anticipate a claim, a single prior source must contain each and every limitation of the claimed invention.

Applicants respectfully aver that the claimed solders are compositions that are distinctly different from the compositions described by Lauto. The compositions of this invention possess entirely different properties from those described by Lauto. The instant amendment and the discussion below clarify these distinct differences.

The claimed protein-based compositions are distinctly different from those described by Lauto because the solders of the invention are "pre-denatured" prior to use in the body (prior to use *in situ*) – in other words, the solders of the invention are partially or completely denatured *ex vivo*, i.e., during the manufacturing of the solder (however, please note that in one aspect, solders of the invention can be further denatured *in situ*). The "at least partial pre-denaturation" or "precooking" of the proteinaceous material causes a relatively homogenous internal bonding, or crosslinking, of the protein (the cross-linking-denaturation effect can be partial or complete). The result of this "pre-denaturation" cross-linking of proteinaceous material is that the claimed compositions do not substantially dissolve in solution, irrespective of the original water content of the mixture of proteinaceous material and solvent. This substantial insolubility is in contrast to the compositions of Lauto, which remain relatively soluble, as discussed, below.

Furthermore, the invention's "pre-denaturation," cross-linking process produces a solder that is effective *in situ* at a relatively low protein concentration, e.g., at least 50%, 60% or 70% protein mixture. The "pre-denatured," cross-linked solder does not substantially dissolve when immersed in saline. The proteinaceous material has been cross-linked (bound to itself) during the pre-denaturation treatment (which can be partial or complete denaturation). Upon immersion in a hydrating solution, the claimed product hydrates and becomes elastic. There is no loss of proteinaceous material (e.g., albumin) to the solution. If the product is removed from solution and dried the amount of proteinaceous material in the product remains unchanged.

In contrast, Lauto does not "pre-denaturate" (cross-link) its solder *ex vivo*. Lauto does not at least partially denature its solder during its manufacture. Thus, Lauto's solder is structurally distinct from the solder of the instant invention.

Because it is not least partially denatured during its manufacture, Lauto's solder is relatively soluble *in situ*. Lauto needs to use high albumin concentration - above 70% - in its solder to significantly reduce solubility and retain the shape of the final albumin product (see, e.g., column 2, lines 54 to 62; column 6, lines 1 to 10, of Lauto). A high albumin concentration was needed to decrease solubility because Lauto did not pretreat (cross-link) their solder before placing it *in situ*. Lauto's albumin product remains relatively soluble, dissolving at a slow rate (see discussion below). In contrast, this is not the case with the biomolecular solder of this invention. The product of the claimed invention is different (and in some cases superior) because the *ex vivo* cross-linking (at least partial pre-denaturation) step makes the proteinaceous solder insoluble and elastic. It is the instant application that for the first time describes cross-linking of proteinaceous solder *ex vivo* before its placement *in situ*.

In situ solubility differences (e.g., in physiologic solution) denote the structural difference between the solder compositions of the instant claimed invention and the composition described by Lauto. The ability (or inability) of Lauto's albumin compositions to retain their shape at different concentrations in saline is discussed in Example 1, columns 5, line 60 to column 6, line 10:

> After preparation, the samples were placed in 0.5 ml of a saturated saline solution, and the solution was shaken every minute for 2 or 3 seconds. Every few seconds the portion of the composition samples that was not yet dissolved was rescued and observed under a dissecting microscope at fifty times magnification. The 56% composition was completely dissolved after only 3 minutes. The 66% composition was observed to lose its shape and was observed to curl severely and fold after 45 seconds. The 70% composition lost its shape and severely twisted and curled after only 85 seconds. In addition, both the 66% and 70% compositions broke very easily when they were pulled apart with fine forceps, as observed under the microscope. The 75% composition, surprisingly, retained its shape and twisted only slightly after 50 minutes in solution. Furthermore, the 75% composition was appreciably more resistant to being pulled apart with fine forceps than were the lower concentration compositions. (emphasis added)

It is clear Lauto's specification that increased albumin concentration was used to reduce the solubility of their albumin product in saline. However, importantly, the albumin product nevertheless dissolves, but at a slower rate when the albumin concentration is increased.

Alternative aspects of the claimed process can use varying *ex vivo* cross-linking (pre-denaturation) conditions, varying *in situ*-denaturation conditions, or both. The temperature of *ex vivo* cross-linking denaturation can be changed to determine and control the amount of internal strength of the solder. For example, a hydrated albumin product denatured at 90°C has different elasticity to a product denatured at 130°C. However, in all embodiments of the instant invention, the final, *in situ* solder is insoluble, unlike the product described by Lauto.

Thus, the present invention found that *ex vivo*-denaturation ("pre-denaturation") can significantly reduce proteinaceous solder solubility in physiologic solution. Varying denaturation temperature can vary the elasticity and internal strength of the solder product independent of initial protein concentration. In practicing the instant invention, initial protein concentration is only chosen to facilitate the desired shape to be formed, not to impart the insolubility property.

The biomolecular solders of the claimed invention are based on entirely different principles – they are made by entirely different methods (incorporating *ex vivo* cross-linking) - when compared to the compositions of Lauto (which are excited *in situ*). The biomolecular solder of the claimed invention possesses entirely different physico-chemical properties when compared to the compositions of Lauto, as evidenced, e.g., by *in situ* solubility. Thus, the compositions of the claimed invention are a different product. The difference is imparted by *ex vivo* cross-linking (complete or partial "pre-denaturation") of the protein to provide a substantially insoluble proteinaceous solder.

Thus, Applicants submit that because Lauto is not a single prior source that contains each and every limitation of the claimed invention and does not teach or suggest the composition or methods of the instant invention the rejection of the claims under 35 U.S.C. §102(e) may properly be withdrawn.

CONCLUSION

In view of the foregoing amendment and remarks, Applicants respectfully aver that the Examiner can properly withdraw the rejection of the pending claims under 35 U.S.C. §112, first and second paragraphs and 35 U.S.C. §102(e). The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Applicants submit concurrently herewith a Petition for 2-month Extension of Time and the appropriate Fee Transmittal for the Petition and the additional claim fees. No other fees are believed to be necessitated by the present response and amendment. However, in the event any such fees are due, the Commissioner is hereby authorized to charge any such fees to Deposit Account No. 03-1952 referencing docket no. 577122000200. Please credit any overpayment to this account.

As noted above, Applicants have requested a telephone conference with the undersigned representative to expedite prosecution of this application. After the Examiner has reviewed the instant response and amendment, please telephone the undersigned at (858) 720-5133.

Dated: October 27, 2004

Respectfully submitted,

By _____

Gregory P. Einhorn
Registration No.: 38,440
MORRISON & FOERSTER LLP
3811 Valley Centre Drive, Suite 500
San Diego, California 92130
(858) 720-5133